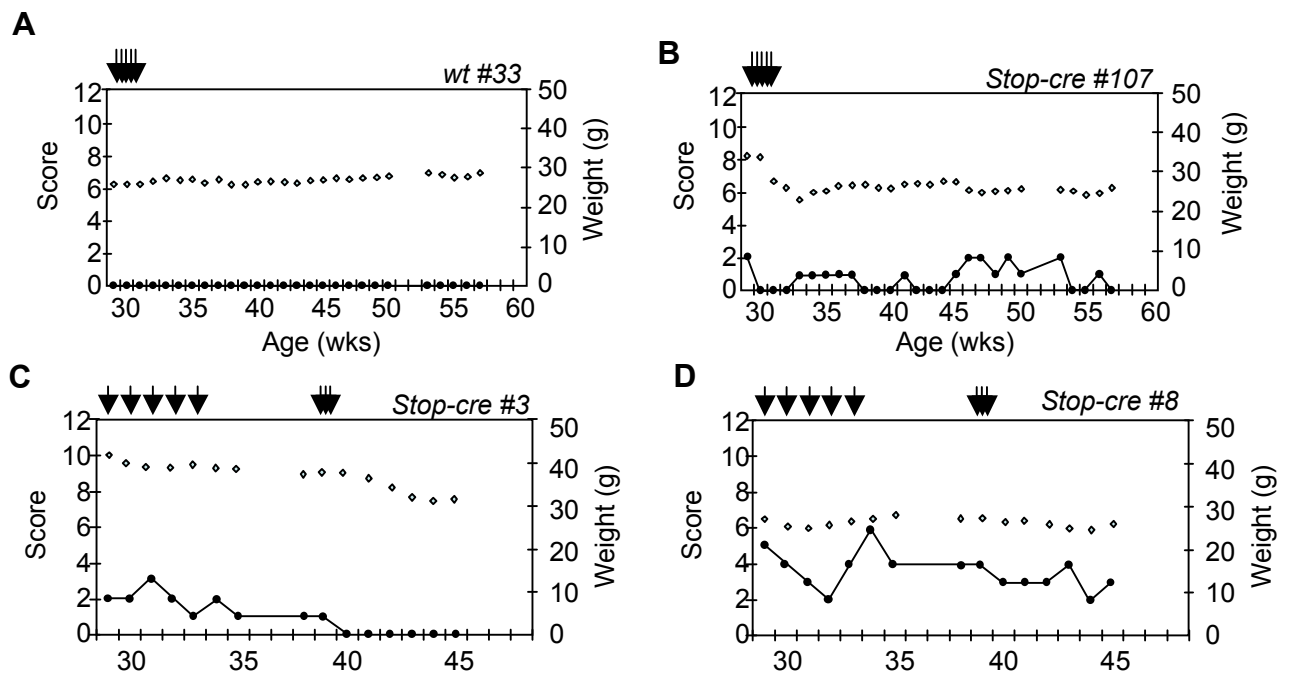


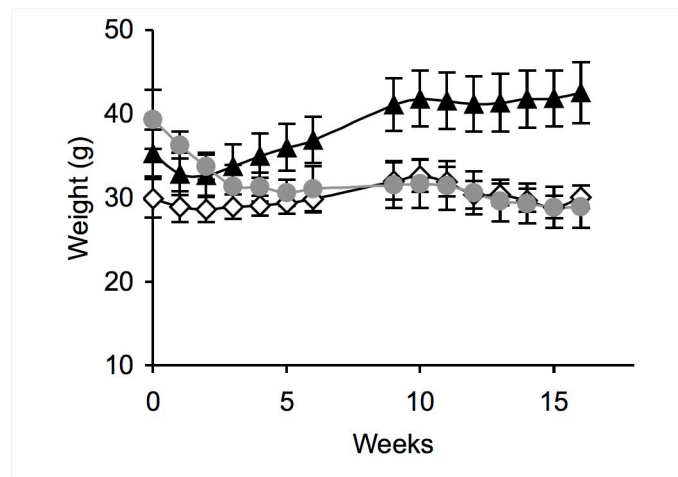
**Supplementary Fig 1.** Examples of symptom score profiles in individual *Mecp2<sup>lox-Stop</sup>, cre-ER* males after a course of TM treatment (arrows). Individual mouse data are aggregated in Fig. 2E.



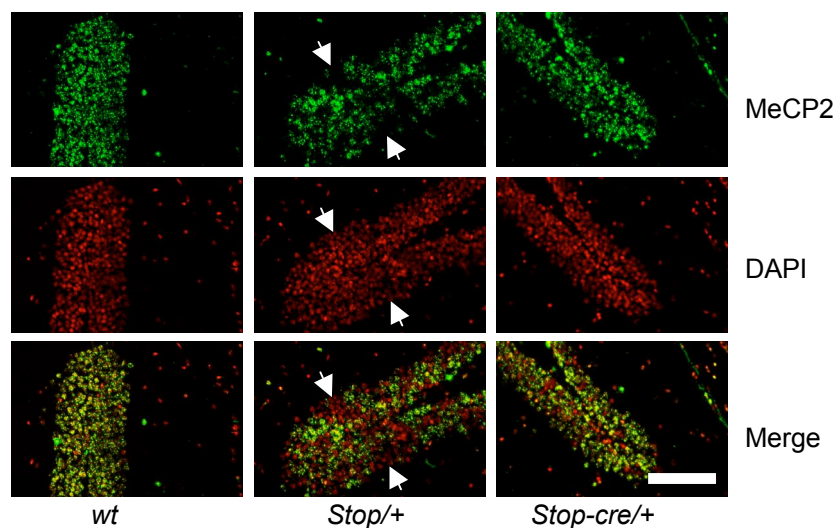
**Supplementary Fig 2.** Symptom/weight profiles of individual *Stop-cre/+* female mice after TM treatment.

A. A typical wildtype female scored zero at all times before and after TM treatment (vertical arrows).

B - D. *Mecp2<sup>lox-Stop/+</sup>, cre-ER* females show degrees of symptom relief. The slight improvement seen in D was the weakest response seen among 10 TM-treated *Stop-cre/+* females.



**Supplementary Fig. 3.** Weight profile of TM-treated *Stop/+cre* females (grey dots;  $n = 5-11$ ) shows progressive approach to weight of wildtype (open diamonds;  $n = 5-6$ ). *Stop/+* control animals (black triangles;  $n = 6-7$ ) show persistent obesity. Measurements began on the day of the first TM injection (zero weeks).



**Supplementary Fig. 4.** High level reactivation of MeCP2 expression in TM-treated *Stop-cre/+* female dentate gyrus suggests that cre-mediated recombination is preferentially targeted to the inactive X chromosome. *Stop/+* female dentate gyrus shows patchy immuno-staining for MeCP2 (middle panels). Blank regions (arrows show two examples) are presumably due to inactivation of the wt allele in a clone of neurons. After reactivation by TM, the great majority of neurons are MeCP2-positive (right panels), but southern blots show that only ~50% of *lox-Stop* alleles have recombined (see Fig. 3F). This could be explained if cre-mediated recombination only occurs on the active X chromosome. All MeCP2-negative neurons must have inactivated the wt allele and would therefore reactivate MeCP2 if cre preferentially targets the active X chromosome. MeCP2-positive neurons must have inactivated the *lox-Stop* allele, but remain MeCP2 positive even though recombination does not delete the *lox-Stop* cassette. This hypothesis would require further experimental testing, but does not affect interpretation of the phenotypic reversal results.